Development of a multiparametric cardiovascular toxicity assay using iPSC derived cardiomyocytes, endothelial cells, and primary cardiac fibroblasts

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Purpose: Unexpected cardiotoxicity underlies high levels of late-stage attrition and post-market withdrawals. Cardiotoxic effects of compounds are predicted using in vitro expression of single cardiac ion channels, in vivo and ex vivo studies. However, these models fail to reflect the complexity of the human cardiac microenvironment. Approximately 70% of the cells in the human heart are non-myocytes with cardiac fibroblasts and vascular cells forming the majority. HiPSC-derived cardiomyocytes have become an attractive platform for capturing the effects of chronic modulators or toxicants and could complement existing assays to improve cardiac safety assessments. To date, there is no validated multi-cellular human-derived in vitro system for assessing drug-induced changes in contractility.

Methods: The baseline function of mono-and co-cultures were assessed using calcium flux, kinetic live cell imaging to assess contractility. Design of Experiments was used to evaluate how specific factors influenced endpoint parameters derived from multiple phenotypic assays.

Results: We successfully implemented design of experiments to test various co-culture combinations. This included optimisation of cell seeding via liquid handling platforms, high-throughput acquisition of beating cardiomyocytes, and derivation of cardiac parameters. Four main factors were found to have a significant effect on cardiac peak amplitude. Our results demonstrate the added value of design of experiments when investigating multi-factor interactions. Moreover, co-culturing with non-myocytes may increase the scope, maturity and predictivity of current assays.